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FORMACRYL

(511) 05 - pharmaceutical, veterinary and hygienic preparations plasters, dressings.

IO - surgical implants; eye prostheses, breast prostheses.

42 - plastic surgery; medical, hygienic and cosmetic care.

(54) PROCESS FOR PRODUCTION OF GEL-LIKE MATERIAL FOR SOFT TISSUES PLASTIC SURGERY

The invention relates to medicine and is intended for use in surgical practice for soft tissues plastic surgery.

Known in the art is application of a 3% polyacrylamide gel (USSR inventorship certificate N 1697756) for completing the volume of a vocal chord.

The main task whose solution is to be addressed by the invention, as being claimed and as set forth in the application resides in creating a material in the form of a gel on the basis of a copolymer of acrylamide that is useful as to its biological and physico-chemical properties for use as such for soft tissues plastic surgery.

The task set is to be solved owing to the fact that offered is a material in the form of a gel for soft tissues plastic surgery, comprising a polyacrylamide and a fluid medium, which according to the invention, comprises, as the polyacrylamide, a copolymer of acrylamide and methylene-bis-acrylamide in a ratio to mass of 100:0.5 - 5.0, the fluid medium is represented by weakly alkaline water, with a ratio of components, wt.%, as follows:

polyacrylamide	1.0 - 8.0
Water	92.0-99.0

and has a pH -value of 6.9 - 8.5, the level of permanganate oxidability not exceeding 1.0 mgO/l and the level of bromination ability not higher than 3.0 mgBr /l.

For the plastic surgery of hypodermic tissues, a gel-like material contains preferably the following ratio of components wt%:

polyacrylamide	1.5 - 2.5
water	97.5-98.5

For the plastic surgery of muscular and glandular tissues a material contains preferably the following ratio of components wt%:

polyacrylamide	4.0 - 8.0
water	92.0 - 96.0

The task set is further solved owing to the fact that claimed is a process for the preparation of a material for the plastic surgery of soft tissues in the form of a water-containing polyacrylamide gel, in which, according to the invention, the copolymerization of an acrylamide is conducted with a methylene-bis-acrylamide in an aqueous medium at a pH of 9.0 - 9.5 in the presence of a peroxide polymerization initiator and, along with this, a reaction mixture is incubated at t = 20-90°C for 2 - 24 hours and then at t = 100-105°C for 2-4 hours.

The polymerization initiator used is represented by ammonium persulfate in an amount of from 0.0006 to 0.03 wt% or hydrogen peroxide in an amount of from 0.1 to 0.3 wt% or both components in any ratio in an amount not exceeding ones as mentioned hereinabove.

For the provision of a reaction mixture pH value, usable water is treated by an electrolysis method.

Now the invention will be described by way of graphic materials (Cf. the drawing) in which is shown the IR-spectrum of a gel material, as proposed, in the region of 4000 - 200 cm^{-1}.

The essence of the invention consists in that, firstly, experimentally selected are polymer-forming components and a quantitative ratio thereof; a fluid medium and the quantitative

ratio of the polymer with the fluid medium providing the density, as required, and material consistence; secondly, selected are conditions for obtaining a gel material which is useful as to its physico-chemical and biological properties for performing the plastic surgery of soft tissues.

The reaction of copolymerization of an acrylamide and a methylene-bis-acrylamide is known (USSR, Inventorship certificate N 1105767). In the process of polymerization there is formed a cross-linked polymer whose structure depends on synthesis conditions: the quantitative ratio of reagents, the qualitative composition of polymerization initiators and temperature conditions.

The claimed process on the account of a reaction mixture incubation in two steps - at lower temperatures first and then at higher temperatures - permits reducing the number of free amino groups (NH_2 radicals) in a polymer, which is corroborated by the graph presented in the drawing of the IR spectrum of the gel-like material as proposed (the material contains 5% of polyacrylamide, wherein 2 wt. parts of methylene-bis-acrylamide are for 100 wt. parts of acrylamide, and 95% of weakly alkaline water; a pH value of 8.0, the level of permanganate oxidability is 0.2 mgO/l, the level of bromination ability is 0.5 mg Br/l; it is obtained with incubation of an initial mixture at $t = 60^{\circ}C$ for 12 hours and then at $t = 100^{\circ}C$ for another 3 hours. As is evident from this spectrum, absent therein are bands of 1620 cm^{-1} responsible for the deformation vibrations of NH radicals and 3200 cm^{-1} and 3600 cm^{-1} responsible for stretching vibrations

of these radicals, which testifies to the fact that in the polymer structure, the contained free NH_2 radicals account for not more than I% of the total functional groups.

Besides this, pathomorphological research studies have shown (Cf. Report N 2 MMA) that the single-stage incubation of a reaction mixture results only at t=30-90°C or only at t= I00-I05°C in obtaining a gel having the level of permanganate oxidability of from 2.0 to 5.0 mgO/l and the level of bromination ability of from 3.0 to 5.0 mg Br/l. On administration of this gel into rats there were observed an inflammatory reaction and sclerosed tissues and also accelerated gel resorption.

The process, as disclosed, further permits eliminating a stage of washing off the resultant material from toxic initial monomers, since the concentration of initial components and polymerization process conditions enable one to obtain a gel devoid of the unreacted monomers, a factor that is confirmed by the test results of the target product.

The acrylamide and methylene-bis- acrylamide are taken suitable for biological purposes and not requiring further purification.

Water is purified by distilling it twice and , then subjected to electrolysis, as it is described in the "Methodic instructions on the preparation of electrochemical activated solutions (neutral anakite) generated in an installation STEL-4M-60-0I for purposes of presterilization purification and sterilization", Moscow, I993.

A gel is produced in the following manner.

For the preparation of a reaction mixture, use is made of distilled-twice water subjected to electrolysis at the voltage

of 220 V, the current intensity of 6A, with a pH value after electrolysis treatment, of from 9.0 to 9.5. An aqueous solution of acrylamide and methylene-bis-acrylamide is prepared in a ratio to mass thereof being between 100:0.5-5.0 and, along with this, the total of the initial monomers in the solution is 1.0-8.0%. Gels with various density and elasticity are obtained by varying the amount of initial monomers in the mixture. The resultant solution is added with polymerization initiators: hydrogen peroxide in an amount of from 0.1 to 0.3 wt.% or ammonium persulfate in an amount of from 0.0006 to 0.03 wt.% or a mixture thereof in any ratio in an amount not exceeding the sum total of peak values thereof. The finished reaction mixture is filtered through bactericidal polymer filter means, brand F8273, with the pore size of 0.45 mm CA/CN, the manufacturer Sigma (USA), and is poured in nitrogen stream in glass containers in the required volumes. The containers are hermetically packed up and placed for incubation at t= 20-90°C for 2-24 hours followed by raising the temperature up to 100-105°C, and the incubation is carried out for another 2-4 hours.

With hydrogen peroxide being present in an incubation medium the latter turns into water and ozone which sterilizes the final product. However, for reliability's sake, the resultant gel is sterilized by autoclaving (t=120°C, p = 1,2 atm.) for 30 minutes.

The following characteristics of the obtainable material have been checked: an index of refraction (according to the methods described in the "Practical course in physical chemistry",

Moscow, I974, pp. 86-97);

a pH value, the level of permanganate oxidability - according to the methods contained in the book "Methodical instructions on sanitation-hygienic evaluation of rubber and latex products of medical designated purposes", Moscow, 1988, pp. 18, I9.

The level of bromination ability - according to the methods described in the "Collection of guide methodical materials for toxicological investigations of polymeric materials and products based thereon of medical purpose", Moscow, Ministry of Public Health of the USSR, 1987, pp. 27-29;

The content of the monomers of acrylamide and methylene-bis-acrylamide - according to the methods described in the "Collection of guide methodical materials on toxicological investigations of polymeric materials and products based thereon of medical purposes", Moscow, Ministry of Public Health of the USSR, I987, pp. 18-25.

The resultant material has the following physico-chemical characteristics:

Appearance	Colorless gel
Refractive index	1.328-1.360
Density	0.9 - 1.2 g/cm^3
pH	6.9 - 8.5
Acrylamide monomer content	absent
Methylene-bis-acrylamide monomer content	absent
Permanganate oxidability level	0.2-1.0 mgO/l
Bromination ability level	Not higher than 3.0 mgBr/l

The sanitation-chemical tests of the claimed material have been conducted in the Institute of Rubber-latex Products, toxicological and pathomorphological investigations - in the Moscow Medical academy named after I.M. Sechenov and in the All-Russia research institute for testing medical equipment under a program developed in the institute. As a result it has been established that the material proposed for soft tissues plastic surgery does not provoke tissue reaction, sensitization of organism, dystrophic and and necrotic changes; it is not mutagenous and is recommended for endoprosthesis and contour plastic surgery (Findings N 3, Report).

The resulting material has the following physico-chemical characteristics:

Appearance	Colorless gel
Refractive index	1.348
pH	7.2
Density	1.0 g/cm^3
Acrylamide monomer content	absent
Methylene-bis-acrylamide monomer content	absent
Permanganate oxidability level	0.4 mgO/l
Bromination ability level	0.1 mgBr /l

The resulting material has the following physico-chemical characteristics:

Appearance	Colorless gel
Refractive index	11.334
pH	8.3

Density	0.95 g/cm^3
Acrylamide monomer content	absent
Methylene-bis-acrylamide monomer content	absent
Permanganate oxidability level	I0.6 mgO/l
Bromination ability level	0.15 mgBr/l

The material under consideration had been used for hypodermic tissue plastic surgery for removing wrinkles from the face. A gel was administered into patient S., aged 47.The operation was performed May 20, I995. Postoperative observation 12 months with periodic examinations once in three months.No inflammatory and allergic symptoms. Patient's cosmetic effect was very good.

The resulting material has the following physico-chemical characteristics:

Appearance	Colorless gel
Refractive index	1.352
pH	8.0
Density	1.2 g/cm^3
Acrylamide monomer content	absent
Methylene-bis-acrylamide monomer content	absent
Permanganate oxidability level	0.2 mgO/l
Bromination ability level	0.05 mgBr/l

The resulting material was used for sural muscle plastic surgery. A gel, I50 g for a muscle, was implanted into patient S., aged 47.

The operation of administering the material proposed was carried out May 20, 1995. Postoperative period of observation 12 months with periodic examinations once in three months. The result: no inflammatory symptoms and edema observed.

According to the patient, a cosmetic effect was good.